4-1-2019

Postmenopausal women with osteoporosis, comparing treatment of oral bisphosphonates to denosumab

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By

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Capstone Project

Submitted to the Faculty of the

Department of Physician Assistant Education

of University of the Pacific

in partial fulfilment of the requirements

for the degree of

MASTER OF PHYSICIAN ASSISTANT STUDIES

April 2019

INTRODUCTION

Osteoporosis is a global health problem that affects more than 75 million people in the United States, Europe, and Japan. Between the United States and Europe, more than 2.3 million people sustain fractures annually due to osteoporosis.[1]

Osteoporosis is a chronic condition characterized by decreased bone mass and deterioration of bone microarchitecture both of which compromise bone strength, predisposing people to fragility fracture.[2] The World Health Organization (WHO) defines severe osteoporosis (established osteoporosis) as a bone mineral density (BMD) 2.5 standard deviations or more below the young adult mean accompanied by one or more fragility fractures. Osteoporosis is more common in women than men, due to women's lower peak bone mass and their declining estrogen levels with age. Peak bone mass occurs around 30 years. Estrogen helps preserve bone mass, but its levels decrease after menopause. As these hormonal levels decrease, bone mass declines and bone weaken, resulting in fractures that often occur with a fall. Many people become bedridden after a fracture which causes secondary complications that can be life-threatening.[1,3]

For those at risk, or for those already diagnosed with osteoporosis, prevention and treatment generally include increasing activities such as weight-bearing exercises, increasing calcium intake, making lifestyle changes and quitting tobacco. These measures often help prevent further bone loss even when pharmacological therapy is started.

Pharmacological intervention for osteoporosis requires continuous treatment with medications that primarily act on the bone resorption component of bone remodeling pathways. Among currently available agents, oral bisphosphonates and subcutaneous injection denosumab are commonly prescribed for osteoporosis.[3] Of the two medications, oral bisphosphonates are considered the first line of treatment. Oral bisphosphonates are traditional antiresorptive agents that contain nitrogen and potently inhibit osteoclast-mediated bone resorption.[4,5] Denosumab is a

subcutaneous (SC) injection given in the amount of 60mg every six months. It is a fully human monoclonal antibody (immunoglobulin G subclass 2 [IgG2]) with high affinity and specificity for human receptor activator of NF-kB ligand (RANKL). It neutralizes the activity of human RANKL, similar to the action of endogenous osteoprotegerin. Denosumab blocks RANKL, inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and increasing bone mass and strength in both trabecular and cortical bone.[3]

For postmenopausal women with osteoporosis, initiating treatment is vital to increasing bone mineral density and avoiding bone fragility, which can lead to fractures. Long-term treatment of osteoporosis in postmenopausal women with bisphosphonates increases bone mineral density. Even though oral bisphosphonates are the most commonly prescribed medication for osteoporosis, a majority of postmenopausal women discontinue bisphosphonate therapy within the first year of treatment due to cost, dose schedules, and side effects, thus, causing poor drug adherence. Evaluation of pharmaceutical treatments for newly diagnosed osteoporosis in postmenopausal women requires comparison of oral bisphosphonates to denosumab in order to assess which pharmacological treatment is better for preventing bone loss or fractures, with the least side effects, and the best overall compliance of treatment within the first few years of treatment.

DISCUSSION

Although postmenopausal women with osteoporosis are usually started on first line-treatment with bisphosphonates, studies show that bone mineral density can also improve with denosumab. Therefore, comparisons of bone mineral density, patient compliance, and medication adherence between bisphosphonates and denosumab were examined. Eleven articles about drug

treatment of postmenopausal women with osteoporosis were found that had sufficient good quality evidence, including some direct comparisons of oral bisphosphonates to denosumab.

Current Evidence

Individual Agents

Bisphosphonates—Oral risedronate was compared to intravenous (IV) ibandronate with the MOVER study. Those patients receiving IV ibandronate achieved significantly higher responder rates than those receiving oral risedronate at all bone sites. The advantage of the study showed that both ibandronate and risedronate helped increase BMD over three years. However, ibandronate was administered by IV route, which made bioavailability 100% versus the oral route of risedronate. Due to administration of the drugs, the outcome shows a greater BMD gain with ibandronate. The study did not examine the overall compliance, adherence, or side effects of oral risedronate, which factors could have resulted in lower BMD compared to ibandronate.[4]

Denosumab—The FREEDOM trial included participants who received 2-5 previous doses of denosumab or placebo and had stopped taking either agent. Fracture incidence was then measured at 7 months or longer after stopping these agents. Both groups sustained an osteoporosis-related fracture during the follow-up period. Many placebo-treated subjects initiated other osteoporosis therapies, specifically a bisphosphonate, during the off-treatment period, which would have been expected to lower their fracture rate. Interestingly, the fracture incidence in the placebo group remained higher compared with the denosumab group. Fracture data during the off-treatment period may have been more difficult to obtain due to the ethics of discontinuing osteoporosis treatment in an individual at increased risk for fracture.[12]

Another study focused on denosumab alone to evaluate medication-taking behavior of 1500 postmenopausal women from Germany, Austria, Greece, and Belgium receiving denosumab. Persistence with adherence to osteoporosis therapy is an important factor in achieving successful treatment outcomes, particularly for fracture reduction. After 12 months, results showed that persistence with denosumab at 12 months was consistently high in all four countries. The persistence observed in the study was at least 1.5-10-fold higher than the persistence found with bisphosphonates in 12-month studies. This study was limited by the different reimbursement for these drugs that the patients received in different countries. In Austria and Germany, participants were fully reimbursed, in Greece patient pay 10-25% of costs, and in Belgium patients pay 16-27% and no overall analyses were performed.[9]

Comparison Studies—Bisphosphonates to Denosumab

A meta-analysis of 11 studies with head-to-head comparisons of 2873 participants on denosumab and 2573 on bisphosphonates suggested that denosumab significantly increased BMD at the hip, femoral neck, lumbar spine, and one-third radius. No significant difference in fracture risk was found between denosumab compared to bisphosphonates. Furthermore, no significant difference between denosumab and bisphosphonates was found for adverse events or withdrawal due to adverse events. The meta-analysis did not report whether the bisphosphonates were taken daily or weekly. These studies were sponsored by pharmaceutical companies, resulting in potential publication bias.[11]

The DAPS included 221 participants open-label study, over a two-year period, that compared adherence of denosumab to oral alendronate once weekly. After one year, more subjects were nonadherent to alendronate compared to denosumab. A total of 198 subjects expressed a preference in treatment of denosumab compared to alendronate tablets and 91.2% chose

denosumab for long-term treatment. Postmenopausal women who received denosumab every six months had significantly better adherence, compliance, and persistence than women who self-administer alendronate orally once weekly. The administration route for denosumab required subcutaneous administration by healthcare professionals with direct evidence of patient adherence to treatment. Follow-up visits with bisphosphonate treatment typically occur annually, however, visits in the study occurred every six months, which could have enhanced adherence. Also, adherence of weekly alendronate treatment required subjects to take at least 80% of the tablets, include two of four doses in the final month, in contrast, denosumab adherence which required administration of 100% of the doses, possibly biasing against denosumab adherence.[5]

An additional study included 875 postmenopausal women were randomized to receive denosumab or oral risedronate. The participants were previously adherent to alendronate therapy and the study focused on transitioning participants to SC denosumab or oral risedronate. After one year, those who transitioned to denosumab, showed an increase of BMD at the total hip compared to those participants on risedronate. Adverse effects occurred in both the risedronate group and the denosumab group, side effects included; hypertension, arthralgia, nasopharyngitis, constipation. The incidence of clinical fractures was similar between the two groups, 17 in the risedronate group and 23 subjects in the denosumab group. Of the fractures acquired throughout the study, 10 subjects from the risedronate group and 6 subjects in the denosumab group had a medical history of osteoporotic fractures at baseline. The study was not designed with adequate statistical power to evaluate anti-fracture efficacy of denosumab and risedronate. Many of the subjects who sustained a fracture on-study had a history of fractures at study entry, that may have increased their risk for future fractures.[6]

Adhering to treatment of osteoporosis for postmenopausal women can be challenging. Higher treatment satisfaction was associated with greater persistence with therapy, which was associated with better outcomes. Pooled data of 1703 postmenopausal women from two international multicenter, randomized, open-label study evaluated patients transitioned from oral daily or weekly bisphosphonates to either denosumab or monthly oral bisphosphonates. At 6 and 12 months, patients in both treatment groups showed improvement from baseline for all four domains of treatment satisfaction but the satisfaction was greater for denosumab than for alendronate. Those with lower satisfaction with osteoporosis treatment were more likely to discontinue/switch medications than women who reported higher satisfaction.[8] Low adherence to long-term therapies result in diminished health benefits and increased health costs. In patients with osteoporosis, nonadherence to medication is associated with increased risk of fracture as compared with those who are adherent.

The DAPS study which included 250 postmenopausal women, compared adherence to subcutaneous denosumab 60mg every 6 months or oral alendronate 70mg once weekly. After year one and two, adherence to denosumab was greater than treatment adherence to alendronate. Adherence rates were higher-than-expected due to participants knowing they were being monitored for adherence during the trial. Also, participants were evaluated by osteoporosis experts at referral centers which may not represent real-world clinical practice for either alendronate or denosumab users.[7]

To evaluate bone mineral density and bone metabolism, a total of 113 postmenopausal women were randomized to receive denosumab or alendronate 70mg once weekly along with vitamin D. After 12 months, BMD increases in the denosumab group were greater than those found in the bisphosphonate group. No changes in serum calcium were observed in either the denosumab

or alendronate group. Limitations of the study included a small sample size. Furthermore, the observational design may have introduced unintentional bias. The baseline characteristics were identical between the two study groups, which was a strength.[3]

Another study provided further evidence that denosumab was superior to bisphosphonates. Four hundred, twenty-five postmenopausal women with osteoporosis completed a trial of denosumab that examined BMD and bone turnover markers. Additionally, the effect of denosumab in bisphosphonate-naïve patients was compared to its effects on patients previously treated with bisphosphonates. Those patients whose densitometric gain was over 3% after one year of denosumab treatment were considered responders. Denosumab increased BMD in both bisphosphonate-prior and bisphosphonate-naïve women. Limitations of this study included a lower number of bisphosphonate-naïve women participating compared to the number of bisphosphonate-prior women. BMD was recorded after one year of treatment without intermediate measurements. BMD measurements were not completed by the same examiner. Most of the women in the bisphosphonate group were switched to denosumab because of poor clinical response to bisphosphonates which imposed bias.[2]

Lastly, an observational study with 78 postmenopausal osteoporotic women examined the effects of switching from daily teriparatide to either oral bisphosphonates or denosumab. After one year, no significant difference was observed between the groups in baseline age, body mass index, rate of prior vertebral fracture, overall BMD, or bone turnover markers. However, although both denosumab and bisphosphonates increased lumbar spine and total hip BMD, bisphosphonates did not increase femoral neck BMD whereas denosumab did. Limitations included small sample size. In addition, oral intake of calcium was not assessed, which may have affected the results.[10]

Efficacy

Bone mineral density was an important marker to measure when comparing bisphosphonates to denosumab. Many of the studies completed baseline readings at three skeletal sites; lumbar spine, femoral neck, and total hip. Numerous results showed greater improvement of bone mineral density with denosumab subcutaneously every six months compared to those on bisphosphonates. Bone mineral density and bone turnover are not the only predictors for risk of fracture, but BMD is important to consider when managing and monitoring osteoporosis. In addition, numerous studies incorporated oral calcium supplementation during the treatment period and the oral calcium was not assessed, which may have affected the results.

Safety

Adverse events where monitored while participants took either bisphosphonates or denosumab. The most frequently experienced adverse events were hypertension, arthralgia, nasopharyngitis, constipation, extremity pain, and back pain. Most of the adverse events in both bisphosphonate and denosumab groups were categorized as being either mild or moderate in severity. Serious adverse events reported with denosumab were osteoarthritis, radius fracture, pubic fracture, cerebral ischemia, cerebrovascular accident, and atrial fibrillation. The serious adverse events reported with bisphosphonates included fibular fracture, breast cancer, and coronary artery stenosis.[5,6]

Persistence to Therapy

Patient compliance and adherence were higher with denosumab than bisphosphonates. The dosing intervals of SC denosumab every six months was preferred among most groups. Due to

daily or weekly dosing schedules for oral bisphosphonates, a high rate of frequently missed or incorrectly-timed doses occurred, resulting in poor medication compliance, adherence and persistence. Those who were treatment-naïve or whose dosing schedules of bisphosphonates were difficult to follow were most likely to take their medication consistently.

SUMMARY

The purpose of the analysis was to evaluate first-line treatment of bisphosphonates compared to denosumab for postmenopausal women with osteoporosis by comparing the bone mineral density, side effects, and overall compliance. Bisphosphonates are currently the most commonly used treatment for osteoporosis and are prescribed as a first-line therapy. Dosing often requires daily, weekly, or monthly doses. Denosumab is a subcutaneous injection that is more efficacious than bisphosphonates and is a long-acting injectable over a six-month period before the next dose. The bone mineral density was compared between the two pharmacological treatments. Bone mineral density increased with either bisphosphonates or denosumab. Many findings showed that denosumab increased bone mineral density more than oral bisphosphonates. Furthermore, no studies were done that examined fracture prevention as an outcome either oral bisphosphonates or denosumab.

Compliance with pharmacologic treatment for osteoporosis is vital. Poor adherence to therapy, difficult dosing regiments, and multiple side effects may limit drug adherence. Poor adherence to therapy is common and is associated with unfavorable outcomes. In addition, if a patient with poor compliance incurs a low-trauma fracture or continues to have low bone mineral density while on treatment, some clinicians may think that the patient failed therapy, and thus, may recommend transitioning to another medication.[6]

The studies reveal advantages of denosumab because of better patient adherence to the medication. Patients preferred denosumab therapy compared to bisphosphonate therapy, resulting in better medication adherence. Thus, denosumab improved bone mineral density over time due to better compliance of the medication.

Accurate bone mineral density measurements may have been limited by short follow up periods, especially since denosumab was only given every six months. Several studies only monitored treatment for one to two years. Some studies included small groups whose participants were aware that adherence and compliance were being monitored, which may have led to higher-than-expected adherence. Lastly, many of the studies did not have adequate statistical power to evaluate for fracture prevention.[6]

The overall goal for treatment of postmenopausal osteoporosis is to reduce the risk of bone fractures. This goal may be achieved by optimizing treatment and, adherence, continuously monitoring the efficacy of treatment, and identifying non-responders quickly so that alternative therapies can be given.[4]

CONCLUSION

In conclusion, when comparing bisphosphonates to denosumab most of the studies showed significant improvement in bone mineral density in those patients taking denosumab. These superior bone mineral density results are most likely due to better compliance. Adherence to therapy is vital because mineral density is associated with fracture risk. While these research studies found that denosumab achieved better results, medical practitioners should be cautious when interpreting these findings because some of those studies were sponsored by pharmacology companies which could introduce bias. Therefore, additional studies not sponsored by industry

are needed to confirm these findings. Furthermore, clinical recommendations can be better supported with longer-term studies examining fracture rates, and investigations that focus on compliance and adverse effects as well as efficacy. Lastly, more head-to-head comparisons of denosumab with bisphosphonates are necessary.

Nonetheless, evidence to date suggests that denosumab is an effective alternative to bisphosphonates for treating osteoporosis in postmenopausal women. Better patient tolerance of denosumab may improve compliance. For those patients who have contraindications to oral bisphosphonates or cannot tolerate their parenteral formulation, denosumab is a valuable option. The costs of denosumab, however, may be prohibitive.

REFERENCES

1. Pai M. Osteoporosis Prevention and Management. *J Obstet Gynecol India*. 2017; 67:237-242.

2. Sanchez A, Brun LR, Salerni H, et al. Effect of Denosumab on Bone Mineral Density and Markers of Bone Turnover among Postmenopausal Women with Osteoporosis. *J Osteoporos*. 2016; 2016:8738959

3. Augoulea A, Tsakonas E, Triantafyllopoulos I, et al. Comparative effects of denosumab or bisphosphonate treatment on bone mineral density and calcium metabolism in postmenopausal women. *J Musculoskelet Neuronal Interact*. 2017; 17:444-449.

4. Nakano T, Yamamoto M, Hashimoto J, Tobinai M, Yoshida S, Nakamura T. Higher response with bone mineral density increase with monthly injectable ibandronate 1 mg compared with oral risedronate in the MOVER study. *J Bone Miner Metab*. 2015; 34:678.

5. Freemantle N, Satram-Hoang S, Tang ET, et al. Final results of the DAPS (Denosumab Adherence Preference Satisfaction) study: a 24-month, randomized, crossover comparison with alendronate in postmenopausal women. *Osteoporos Int*. 2012; 23:317-326.

6. Roux C, Hofbauer LC, Ho PR, et al. Denosumab compared with risedronate in postmenopausal women suboptimally adherent to alendronate therapy: efficacy and safety results from a randomized open-label study. *Bone*. 2013; 58:48.

7. Kendler DL, Macarios D, Lillestol MJ, et al. Influence of patient perceptions and preferences for osteoporosis medication on adherence behavior in the Denosumab Adherence Preference Satisfaction study. *Menopause*.2013; 21:25.

8. Palacios S, Agodoa I, Bonnick S, et al. Treatment satisfaction in postmenopausal women suboptimally adherent to bisphosphonates who transitioned to denosumab compared with risedronate or ibandronate. *J Clin Endocrinol Metab*. 2015; 100:487.

9. Hadji P, Papaioannou N, Gielen E, et al. Persistence, adherence, and medication-taking behavior in women with postmenopausal osteoporosis receiving denosumab in routine practice in Germany, Austria, Greece, and Belgium: 12-month results from a European non-interventional study. *Osteoporos Int*. 2015; 26:2479-2489.

10. Ebina K, Hashimoto J, Kashii M, et al. The effects of switching daily teriparatide to oral bisphosphonates or denosumab in patients with primary osteoporosis. *J Bone Miner Metab*. 2017; 35:91-98.

11. Wu J, Zhang Q, Yan G, Jin X. Denosumab compared to bisphosphonates to treat postmenopausal osteoporosis: a meta-analysis. *J Orthop Surg Res*. 2018; 13:3.

12. Brown JP, Roux C, Torring O, et al. Discontinuation of denosumab and associated fracture incidence: analysis from the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial. *J Bone Miner Res*. 2013; 28:746-752.